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Synthesis of HCV Replicase Inhibitors: Base-Catalyzed Synthesis of Protected α-Hydrazino Esters and Selective Aerobic Oxidation with Catalytic Pt/Bi/C for Synthesis of Imidazole-4,5-dicarbaldehyde

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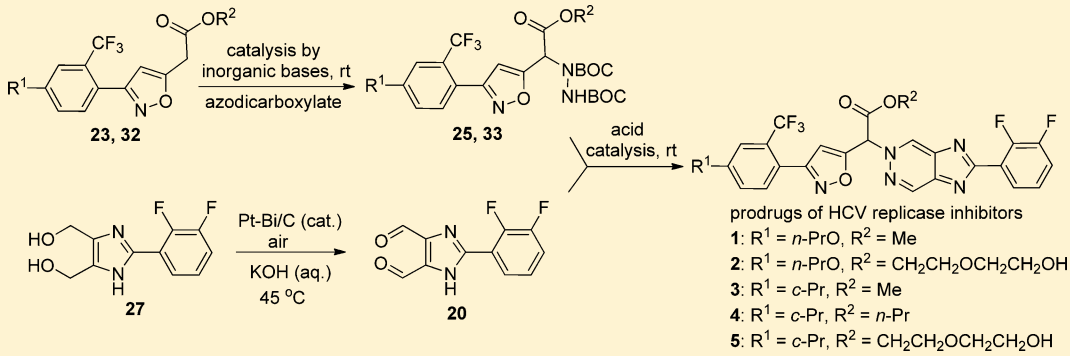
Supporting Information



ABSTRACT: A robust convergent synthesis of the prodrugs of HCV replicase inhibitors **1**−**5** is described. The central 5*H*-imidazo[4,5-*d*]pyridazine core was formed from acid-catalyzed cyclocondensation of an imidazole-4,5-dicarbaldehyde (**20**) and a α-hydrazino ester, generated in situ from the bis-BOC-protected precursors **25** and **33**. The acidic conditions not only released the otherwise unstable α-hydrazino esters but also were the key to avoid facile decarboxylation to the parent drugs from the carboxylic ester prodrugs **1**−**5**. The bis-BOC α-hydrazino esters **25** and **33** were prepared by addition of ester enolates (from **23** and **32**) to di-*tert*-butyl azodicarboxylate via catalysis with mild inorganic bases, such as Li_2CO_3. A selective aerobic oxidation with catalytic 5% Pt−Bi/C in aqueous KOH was developed to provide the dicarbaldehyde **20** from the diol **27**.

INTRODUCTION

Hepatitis C is a liver disease caused by the hepatitis C virus (HCV). According to the World Health Organization, about 150 million people are chronically infected with HCV, and more than 350000 people die every year from HCV-related liver diseases.[1] Until the recent FDA approvals of boceprevir and telaprevir, the standard therapies only provided about 50% response rates for infections with HCV of genotype 1, the prevalent type of HCV infection in the United States.[2] The emergence of drug resistance is a major concern for HCV treatment. There is a strong need to discover and develop new therapies which have novel modes of action and resistance profiles. HCV replicase proteins are essential for HCV replication. The inhibition of replicases has been recently explored as a potential mechanism for treatment of HCV infection.[3] Recently, in our HCV drug discovery program, compounds **1**−**5**, shown in Scheme 1, were identified as the carboxylic ester prodrugs of their corresponding noncarboxylic parents as potent inhibitors of HCV replicases.[4]

The aromatic rings of prodrugs **1**−**5** and their parent drugs are designated rings A−E, shown in Scheme 1, with the 5*H*-imidazo[4,5-*d*]pyridazine core being referred to as the CD ring. The original medicinal chemistry synthesis of compounds **1**−**5** is shown in Scheme 2. The synthesis started with a Grignard addition of ethynylmagnesium bromide to diethyl ketomalonate **8** to prepare propargyl alcohol **9**.[5] A [3 + 2] cycloaddition between the acetylene and a nitrile oxide, generated from oxime **10** and *N*-chlorosuccinimide (NCS) followed by triethylamine, provided isoxazolylmalonate **11**.[6] Hydrolysis of the diesters and monodecarboxylation gave the glycolic acid product **12**. After esterification to the methyl ester **13**, the α-hydroxyl group was activated as mesylate **14**, which was then converted to bromide **15**. Only the α-bromo ester was sufficiently reactive for the final displacement by pyridazine **16** to give the prodrug **1**. The main drawback of this approach was that the last step incorporating the CD ring had a tendency to generate the decarboxylated product **6**, due to the need for a base and a polar solvent for this slow reaction. In a scale-up to produce prodrug **1** with input of 218 g of bromoacetate **15**, the ratio **1**/**6** (prodrug/

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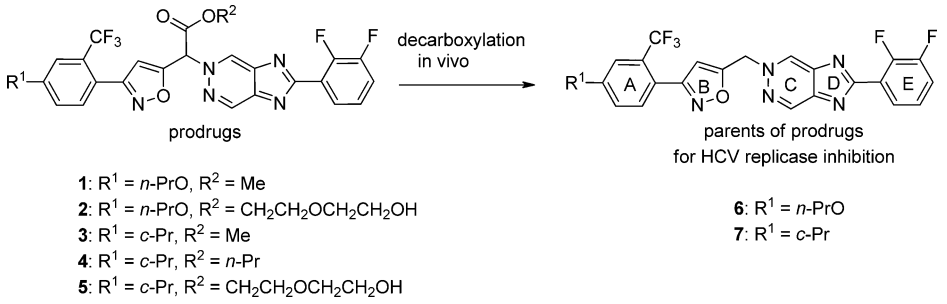
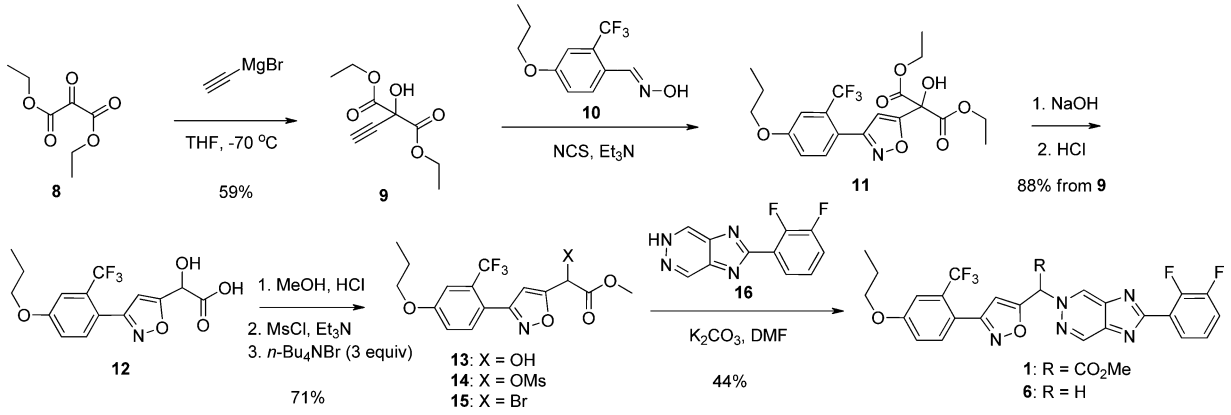
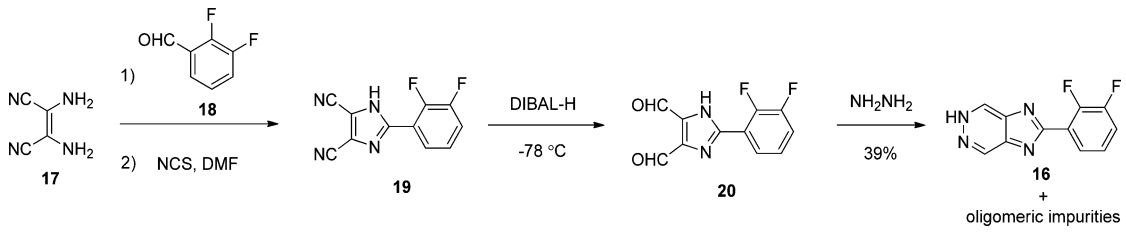
Scheme 1. Structures of Prodrugs 1−5 and Corresponding Parent Drugs



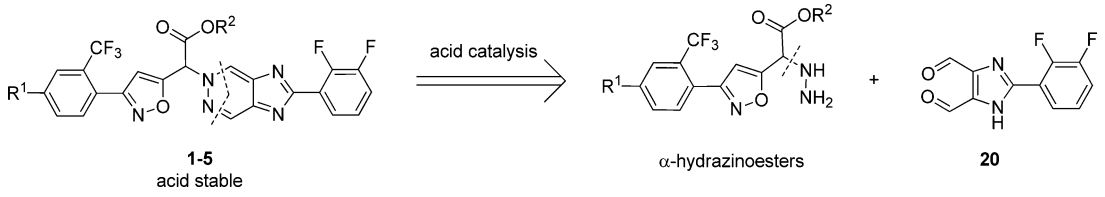
Scheme 2. Previous Synthesis of Prodrug 1 and the Issue of Decarboxylation to Parent 6



Scheme 3. Previous Synthesis of Imidazopyridazine 16 (CD Ring)



Scheme 4. Strategy for Convergent Synthesis of Prodrugs 1−5 from α-Hydrazino Esters



parent) was 7/1, and that led to only a 44% yield of prodrug **1** from **15**. In addition to the requirement for low-temperature conditions, low overall yield and potential genotoxicity of compounds like **14** and **15**, this approach also required fully elaborated pyridazine CD ring **16**, which in itself was very challenging to synthesize (Scheme 3).

The synthesis of imidazopyridazine **16** (CD ring) was relatively short starting from **17**, but the reduction of dinitrile **19** provided dialdehyde **20** in only 60−80% purity. Reaction of the dialdehyde with hydrazine further complicated the chemistry by generating several insoluble oligomeric impurities which could not be removed by chromatography or crystallization, resulting in only a 39% yield of **16** with poor purity. Because of these aforementioned process issues and the urgent need for large amounts of prodrugs **1**−**5**, a new synthetic strategy was envisioned, as shown in Scheme 4. The 5*H*-imidazo[4,5-*d*]pyridazine core in **1**−**5** could be generated from the condensation of α-hydrazino esters and dialdehyde **20**. The use of substituted hydrazine derivatives was expected to avoid the formation of oligomers in comparison with the use of hydrazine in the previous synthesis. The acidic catalysis would not only facilitate the cyclocondensation but also be advantageous in comparison to the basic conditions which led to decarboxylation of the prodrugs to the corresponding parent drugs. The overall efficiency and robustness of our new synthesis would depend on the efficient preparation of the α-hydrazino esters and dialdehyde **20** as well as smooth

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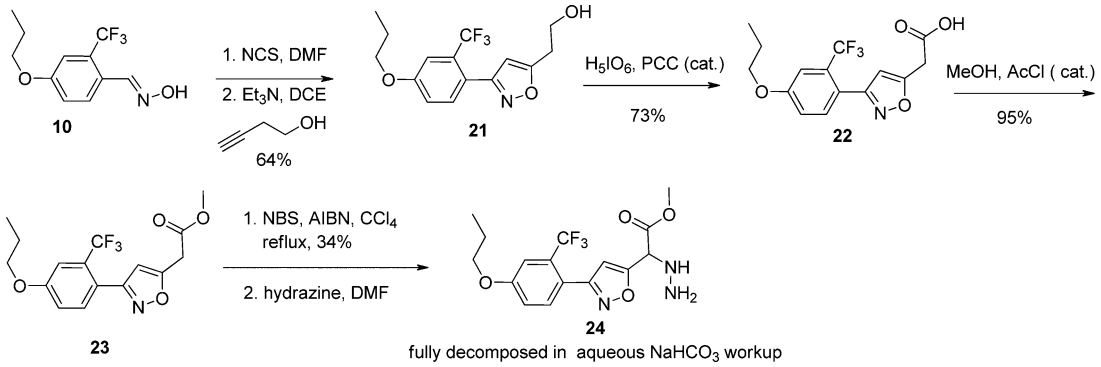
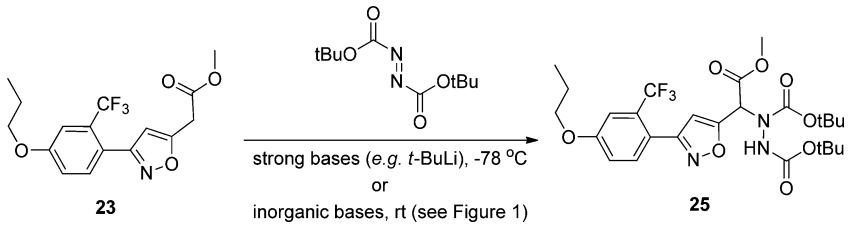
Scheme 5. Synthesis of Labile α-Hydrazino Ester 24



Scheme 6. Synthesis of Bis-BOC-Protected α-Hydrazinoacetate 25 from Ester 23



cyclocondensation to form the pyridazine ring (CD ring system).

We herein report a practical approach to stable forms of α-hydrazino esters and also a new synthesis of dialdehyde **20**. The acid-catalyzed coupling of the α-hydrazino esters and the dialdehyde provided a robust approach to the 5*H*-imidazo[4,5-*d*]pyridazine system, and the prodrugs of HCV replicase inhibitors were synthesized in kilogram quantities.

RESULTS AND DISCUSSION

Our first attempt to synthesize a α-hydrazino ester is shown in Scheme 5. Oxime **10**, prepared from the corresponding aldehyde precursor and hydroxylamine, was chlorinated with NCS and the resultant chlorooxime was treated with 3-butyn-1-ol in the presence of triethylamine to give isoxazolylethanol **21**.[6] Oxidation with periodic acid in the presence of 5 mol % of pyridinium chlorochromate (PCC)[7] provided carboxylic acid **22**, which was then converted to methyl ester **23** with catalytic HCl, generated from methanol and acetyl chloride. Treatment with *N*-bromosuccinimide (NBS)[8] and displacement of the α-bromoacetate intermediate with hydrazine were low-yielding processes, due to product instability under the reaction conditions. The α-hydrazinoacetate **24** decomposed to multiple products within a few minutes when washed with aqueous $NaHCO_3$. The facile formation and the high reactivity of the enolate from the α-hydrazinoacetate **24** were believed to be the reason for multiple products from the reaction as well as the decomposition observed in workup.

The instability of the α-hydrazino ester prompted us to explore a protected form of the compound. We were particularly interested in the bis-*tert*-butyloxycarbonyl (BOC) form **25** (Scheme 6). The active hydrazinoacetate could be released in situ in the presence of an acid.[9]

The acidic conditions were also expected to catalyze the formation of the imidazopyridazine (CD ring system) between the substituted hydrazine and a dialdehyde to avoid oligomeric side products found in the previous synthesis when hydrazine was used, as shown in Scheme 3.

α-Hydrazino esters similar to **25** are known in the literature: they are typically prepared from addition of preformed enolates to dialkyl azodicarboxylates. The enolates are typically formed at low temperatures (as low as −78 °C) with a strong base such as lithium hexamethyldisilazide (LiHMDS),[10] *tert*-butyllithium, or *n*-butyllithium,[11] prior to addition to dialkyl azodicarboxylates. A base screening study was carried out for the α-hydrazination of ester **23** by di-*tert*-butyl azodicarboxylate in order to identify conditions more amenable to scale-ups, such as mild bases, room temperature, and avoidance of preformed enolates (Scheme 6). From the screening, inorganic bases were found to be more suitable to effect the hydrazination and in the meantime minimize loss of product from further side reactions, such as the Claisen reaction and bis-hydrazination. Organic amine bases such as triethylamine and 1,8-diazabicycloundec-7-ene (DBU) also were able to give hydrazino product but led to significant byproduct formation before all of the starting ester **23** was consumed.

Within the inorganic bases screened, only the weaker and less soluble bases, Li_2CO_3 in particular, were found to be efficient in screening, as shown in Figure 1. The stronger bases (Cs_2CO_3, K_3PO_4, and K_2CO_3) depleted the starting ester **23** without much desired product **25** at the end of the reaction, as measured by HPLC analysis of the reaction mixture. In those reactions, di-*tert*-butyl azodicarboxylate was also fully consumed. A byproduct in the presence of strong bases was identified by LCMS analysis as bis-hydrazination from addition of product **25** to another 1 equiv of di-*tert*-butyl azodicarboxylate.

The reaction with Li_2CO_3 was heterogeneous, due to the partial solubility of Li_2CO_3 in DMF at ambient temperature. Although both stoichiometric and catalytic amounts of Li_2CO_3 worked well to prepare crystalline **25**, the catalytic amount allowed better process control on a large scale. The use of a stoichiometric amount of the base could lead to bis-hydrazination and some decomposition, if the process

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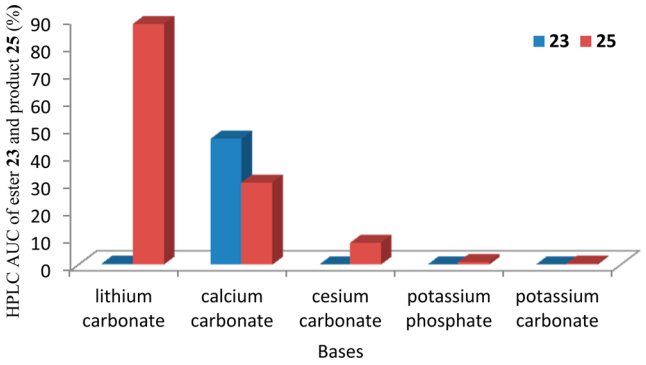
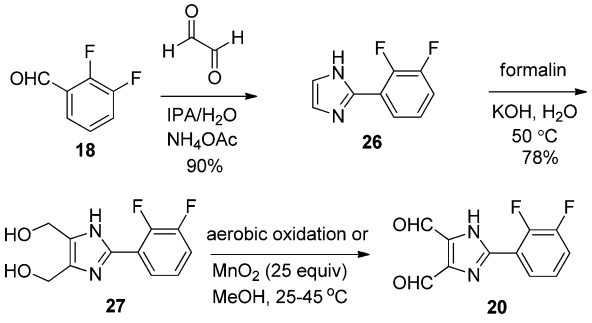


Figure 1. Effect of inorganic bases (2 equiv) for the preparation of **25** from the reaction of **23** and di-*tert*-butyl azodicarboxylate (1 equiv) in DMF (10 vol) at 25 °C for 35 min.

continued after consumption of the starting materials in the presence of a slight excess of di-*tert*-butyl azodicarboxylate. We believe that Li_2CO_3 is uniquely suitable for the process because of its low basicity and solubility that made it possible to avoid further reactions and decomposition of the α-hydrazinoacetate product.[12] Lithium as a common counterion for enolates may be capable of chelation between the enolates and the azo double bond of di-*tert*-butyl azodicarboxylate as in an aldol reaction, which could offer another explanation for the superiority of Li_2CO_3 to other carbonates mentioned above. The robustness of the process was subsequently demonstrated in the preparation of a related compound on a 20 L scale with 5% Li_2CO_3 (vide infra).

To implement the synthetic strategy we laid out in Scheme 4, an efficient new synthesis of dialdehyde **20** was required. This was achieved by a new sequence starting from aldehyde **18**, as shown in Scheme 7.

Scheme 7. Synthesis of Dialdehyde 20 from 2,3-Difluorobenzaldehyde



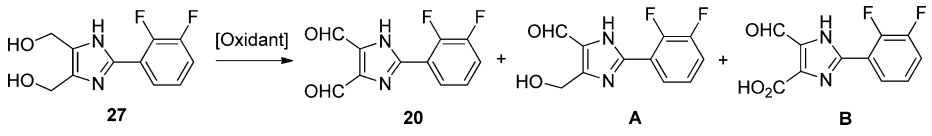
Imidazole **26** was prepared in 90% yield from treatment of **18** with 40 wt % aqueous glyoxal in the presence of excess ammonium acetate.[13] Bis-hydroxymethylation with formalin and aqueous KOH gave diol **27** in 78% yield.[14] The oxidation of the diol to dialdehyde **20** was challenging, due to the formation of various byproducts (Scheme 8). The difficulty resulted from underoxidation to form **A** and overoxidation to monocarboxylic acid **B**. There were also very small amounts of lactol and lactone derived from internal cyclization of **A** and **B**, respectively. These side products rendered most common methods for oxidation of an alcohol to an aldehyde ineffective for the preparation of dialdehyde **20** from diol **27**. We had some success with manganese dioxide in methanol, which is well-known for the oxidation of benzylic type alcohols to aldehydes.[15] The process (>25 equiv of MnO_2 in methanol) was at one point scaled up to prepare **20** in 69% yield. In order to process 600 g of **27**, however, 5.4 kg (25 equiv) of MnO_2 was required and an additional 300 g was added to drive the oxidation to completion (see method A for **20** in the Experimental Section). The weight of the manganese waste was about 10 times that of the product. The safety issue and waste problem from the use of such a large excess of MnO_2 prompted us to look for a more sustainable solution. Oxidation with oxygen or air has attracted significant attention as a sustainable green solution to the oxidation of alcohols to aldehydes and carboxylic acids.[16] The processes often uses a heterogeneous system involving Pt, Pd, Ru, and some other metals.[16b]

A 106-reaction screening of the oxidation was carried out to identify a suitable catalyst and conditions. In addition to supported Pt, Pd, and Ru, Bi was also included in the screening. Bi and Pb are frequently used as promoters when Pt or Pd is the active catalyst on carbon or alumina supports.[17] In addition to the metal types, the solvent, catalyst loading, water amount, and NaOH/KOH equivalents were also varied in the initial screening. The desirability of the reaction conditions was assessed according to HPLC analysis for the amounts of alcohol **27**, dialdehyde **20**, and monoalcohol **A** (underoxidation) and monocarboxylic acid **B** (overoxidation).[18] From the screening, it was found that the bimetallic catalyst system containing 5% Pt, 5% Bi/C (purchased from Evonik Industries) was uniquely effective for the oxidation of imidazole diol **27**. The use of aqueous KOH with MeCN proved critical for the success of the aerobic oxidation to minimize side products. The monoaldehyde **A** and carboxylic acid **B** were generated in <5% quantities under several conditions and in one instance (reaction 104) were not observed on following conditions similar to those shown in Scheme 9.[18]

The amount of oxygen in air (~21%) was sufficient for the oxidation. At a lower oxygen level with 5% oxygen in nitrogen, the reaction stalled at the monoaldehyde stage (product **A**, Scheme 8) when MeCN was used as the solvent. THF was found to be a better solvent than MeCN for full conversion of diol **27** at the 5% oxygen level, but the product was accompanied by relatively large amounts of overoxidation product **B** (Scheme 8).

Under the optimized conditions as shown in Scheme 9, dialdehyde **20** was produced in 85% AUC along with 7% of monoaldehyde **A** and 4% of monocarboxylic acid **B**. Because of the low solubility of the dialdehyde **20** and the side products, the crude product, after removal of the heterogeneous catalyst,

Scheme 8. Mixture of Products in Oxidation of Diol 27 To Prepare Dialdehyde 20



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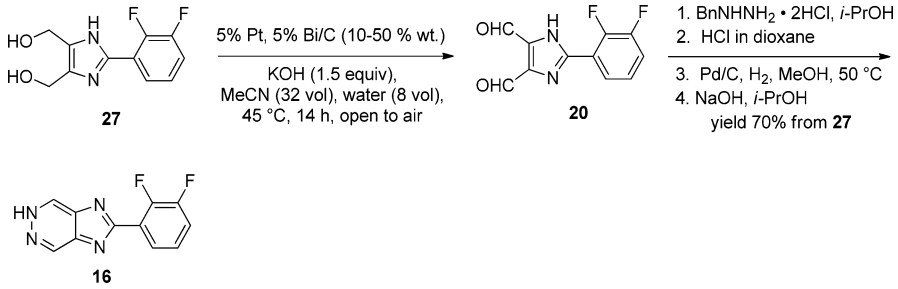
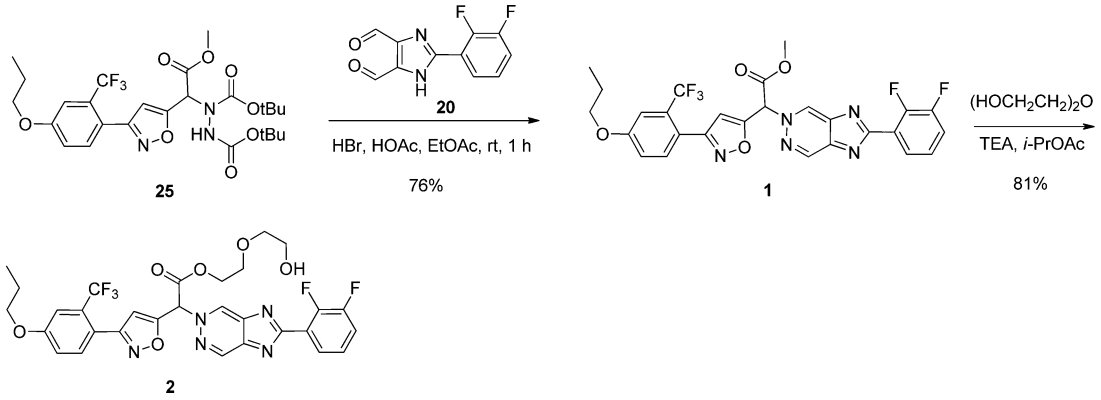
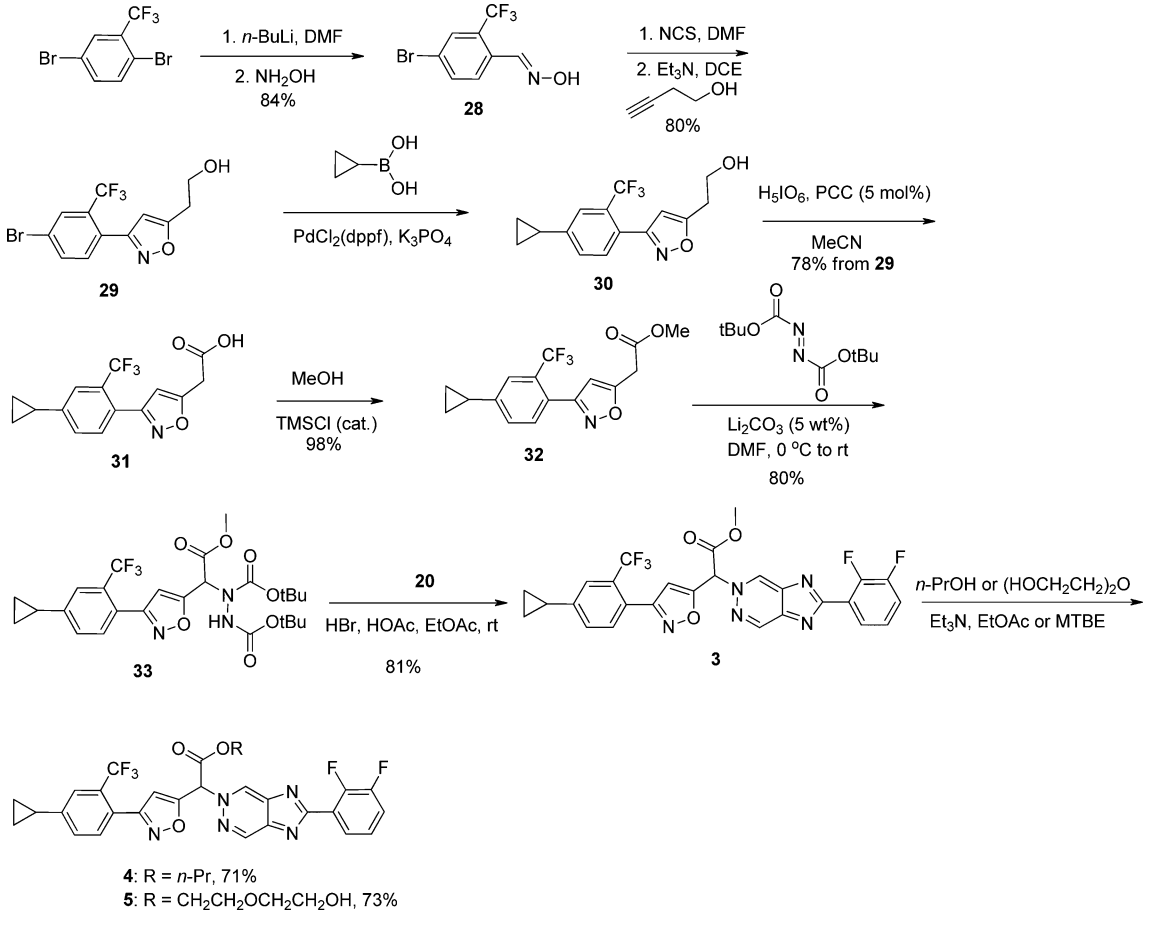
Scheme 9. Optimized Aerobic Oxidation and Conversion of Dialdehyde 20 to CD Ring 16



Scheme 10. Synthesis of Prodrugs 1 and 2 via Cyclocondensation of Dialdehyde 20 and an in Situ Generated α-Hydrazino Ester



Scheme 11. Synthesis of Prodrugs 3−5 on a Large Scale



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was used directly in reactions to prepare compounds **16** (Scheme 9) and **1** (Scheme 10). The mechanism for the oxidation of alcohols by a supported Pt-group metal, the Bi promoter effect, and the roles of bases and water in the aerobic oxidation have been reviewed by Mallat and Baiker.[16b]

As a proof for the efficiency of the aerobic oxidation, dialdehyde **20** was converted to **16** via a crystalline HCl salt of a *N*-benzylpyridazine intermediate, as shown in Scheme 9. The overall 70% yield of CD ring **16** from diol **27** compared favorably to the 49% overall yield of **16** from the same diol starting material by MnO_2 oxidation (69% yield on the MnO_2 oxidation step alone) or the preparation of **16** from 2,3-diaminomaleonitrile shown in Scheme 3. From the point of sustainability, the aerobic oxidation in MeCN/water generated merely about 5 wt % of metal waste relative to the input substrate, in comparison to about 1000 wt % for the MnO_2 oxidation in MeOH. Because of the unexpected project cancellation, the scale-up of the aerobic oxidation beyond the 2 g scale, as described in method C for compound **20**, was halted.

The cyclocondensation with α-hydrazinoacetate was carried out under acidic conditions to generate the 5*H*-imidazo[4,5-*d*]pyridazine core, as shown in Scheme 10. It was apparent that an acid was needed to release the α-hydrazinoacetate intermediate (**24**; structure shown in Scheme 5). In our initial test, 4 vol of 2:1 trifluoroacetic acid (TFA)/CH_2Cl_2 was added to compound **25** at room temperature in the absence of dialdehyde **20**. Formation of α-hydrazinoacetate **24** was observed by LC-MS (MW 373) after 20 min, and there were also small amounts of the two transient mono-BOC intermediates. Attempts to isolate **24** by extractive workup in the presence of aqueous $NaHCO_3$ led to decomposition of **24** to unknown degradants. An acid screening was then carried out with 4 M HCl in 1,4-dioxane, 1 M HCl in HOAc, 33% HBr in HOAc, 10% aqueous H_2SO_4, and 4 M aqueous HCl, again in the absence of aldehyde **20**. HCl in 1,4-dioxane or HOAc after 3 h led to decomposition of the initially formed **24**. The aqueous acids were not strong enough to deprotect **25** at acceptable reaction rates at room temperature. Only the HBr/HOAc condition provided a fast reaction and also avoided decomposition. Given that our goal was the synthesis of the imidazopyridazine and the stability of α-hydrazinoacetate **24** was low in both bases and under some acidic conditions, no further effort was made to isolate **24** as a free base or HBr salt.

When the HBr/HOAc conditions (4 equiv of HBr in HOAc) were applied to **25** in the presence of dialdehyde **20**, the reaction was complete within 1 h at room temperature (Scheme 10). No intermediate α-hydrazinoacetate **24** was detected by HPLC during the reaction, and the two mono-BOC intermediates were below 1% in any of the process monitoring samples. The acidic conditions efficiently catalyzed the hydrazine−dialdehyde condensation, leading to a very clean reaction. Crystalline methyl ester prodrug **1** was isolated in 76% yield.

The use of the substituted hydrazine for imidazopyridazine synthesis with the dialdehyde also avoided oligomeric side products which would form from the use of hydrazine itself. Methyl ester **1** was readily converted to other ester prodrugs such as the bis(ethylene glycol) analogue **2** in the presence of an excess of bis(ethylene glycol) with triethylamine as the catalyst.

The robustness of the chemistry developed for compounds **1** and **2** was further demonstrated in the synthesis of prodrugs **3**−**5**, as shown in Scheme 11. All steps were run in 20 L fixed equipment.

■ CONCLUSIONS

Robust and efficient syntheses of the prodrugs of HCV replicase inhibitors were developed featuring a novel synthesis of the 5*H*-imidazo[4,5-*d*]pyridazine core from bis-BOC-protected α-hydrazino esters and a 4,5-imidazoledialdehyde with acid catalysis. The bis-BOC α-hydrazino esters, latent forms of the otherwise unstable α-hydrazino esters, were prepared via a base-catalyzed addition of esters to di-*tert*-butyl azodicarboxylate at ambient temperature without preformation of ester enolates. The use of a catalytic amount of an inorganic base proved to be the key to avoid side reactions associated with active enolates, and the preparation was advantageous in comparison to typical α-hydrazination of ester enolates at low temperature with a stoichiometric amount of a strong base. This approach was also much cleaner than the previous synthesis of α-hydrazino esters through nucleophilic displacement of α-bromo esters by hydrazine. A unique heterogeneous aerobic oxidation of a diol with catalytic Pt/Bi/C in the presence of KOH was developed to synthesize a 4,5-imidazoledialdehyde required for the synthesis of the imidazopyridazine ring. The aerobic oxidation also generated significantly less metal waste over the MnO_2 oxidation in MeOH.

■ EXPERIMENTAL SECTION

General Procedure. All reactions were run under nitrogen. Heating and cooling were provided through jacketed media controlled by a Huber unit for all 20 L reactors. Smaller reactors were heated by a heating mantle, and the temperature was controlled by a thermocouple. Unless otherwise specified, concentration by rotary evaporation or distillation was carried out under house vacuum of 12−50 Torr. Melting points were recorded in an OptiMelt Automated Melting Point System from Stanford Research Systems and were not corrected. NMR spectra were recorded in a Bruker 500 MHz spectrometer. The analyzer used for HRMS was an Orbitrap from Thermo Scientific (Thermo Scientific LTQ-Orbitrap Discovery XL).

4-(Propyloxy)-2-(trifluoromethyl)benzaldehyde Oxime (10). In a 20 L reactor were successively added 598 g (5.33 mol) of potassium *tert*-butoxide, 3.3 L of toluene, 0.60 L (7.99 mol) of *n*-propanol, and 0.65 L of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU). The mixture was stirred at 50 °C for 30 min. The resultant clear solution was treated with 650 g (2.66 mol) of 1-bromo-4-fluoro-2-(trifluoromethyl)benzene and stirred at 50 °C for 30 min. After being cooled to 25 °C, the reaction was quenched with 3.3 L of water. Layers were separated, and the toluene layer was washed with 4 × 3.3 L of water to remove residual DMPU. The toluene layer was concentrated in vacuo to 1.5 L. About 3.3 L of THF was added, and the solution was concentrated to about 1.5 L to azeotropically remove any residual water. The crude 1-bromo-4-propoxy-2-(trifluoromethyl)benzene thus prepared was further diluted with 3.3 L of THF and used directly for the next step without further purification.

To the above solution was added 4.00 L (8.00 mol) of isopropylmagnesium chloride (2 M in THF). After being heated to 35 °C and stirred for 30 min, the reaction mixture was cooled to 0 °C and treated with 681 g (9.32 mol) of DMF over 15 min. The mixture was warmed to 25 °C and stirred for 30 min. The reaction was quenched with 6.6 L of 1 M aqueous citric acid solution over 15 min, followed by addition of 3.3 L of methyl *tert*-butyl ether (MTBE). Layers were separated, and the organic layer was washed with 3 × 3.3 L of water and concentrated to about 1.5 L in vacuo. To the solution was added 3.9 L of EtOH, and the mixture was further concentrated to about 3.3 L to remove residual THF and MTBE. The crude 4-

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propoxy-2-(trifluoromethyl)benzaldehyde thus prepared was used in the next step without further purification.

To the above solution was added 471 mL (7.99 mol) of hydroxylamine (50% in water). The reaction mixture was heated to 35 °C and stirred for 30 min. The reaction was quenched with 2.0 L of water and cooled to 20 °C. After crystallization had occurred, an additional 2.0 L of water was added. The solids were filtered, washed with 1.3 L of water, and dried in vacuo at 85 °C to give 521 g (79%) of oxime **10** as a crystalline white solid: mp 107.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (d, J = 5.0 Hz, 1 H), 7.93 (d, J = 10.0 Hz, 1 H), 7.22 (d, J = 5.0 Hz, 1 H), 7.07 (dd, J = 5.0, 10.0 Hz, 1 H), 4.00 (t, J = 5.0 Hz, 2 H), 1.86 (tq, J = 5.0, 7.5 Hz, 2 H), 1.08 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 147.0, 129.8 (q, J = 31.3 Hz), 128.9, 123.7 (q, J = 272.5 Hz), 121.9, 117.8, 112.3 (m), 70.0, 22.4, 10.4; HRMS (ESI) m/z calcd for $C_{11}H_{13}F_3NO_2$ (MH^+) 248.0893, found 248.0892.

2-{3-[4-(Propyloxy)-2-(trifluoromethyl)phenyl]-5-isoxazolyl}-ethanol (21). A stirred solution of 34.0 g (138 mmol) of the oxime **10** in 250 mL of DMF was cooled to 0 °C, followed by addition of 19.2 g (144 mmol) of NCS over 2 min. After being stirred for 2 h, the solution was diluted with 400 mL of EtOAc, washed with 2 × 250 mL of water and 150 mL of brine, dried over Na_2SO_4, and concentrated in vacuo to give 44.7 g of the crude chloro intermediate.

The crude intermediate was dissolved in 360 mL of 1,2-dichloroethane and treated with 14.5 g (208 mmol) of 3-butyn-1-ol and 29.0 mL (208 mmol) of triethylamine. Precipitation of the TEA–HCl salt was immediately observed. The suspension was heated to reflux to form a solution. After being stirred for 2 h, the solution was cooled to room temperature, diluted with 400 mL of DCM, washed with 2 × 250 mL of water and 200 mL of brine, dried over Na_2SO_4, and concentrated in vacuo to afford 42.0 g of crude alcohol **21** as a viscous yellow oil. Chromatography on silica gel and elution with 20% EtOAc in hexanes provided 27.5 g (64%) of alcohol **21** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, J = 10.0 Hz, 1 H), 7.29 (m, 1 H), 7.09 (dd, J = 5.0, 10.0 Hz, 1 H), 6.28 (s, 1 H), 3.99 (m, 4 H), 3.06 (t, J = 5.0 Hz, 2 H), 2.51 (m, 2 H including water H), 1.84 (tq, J = 5.0, 7.5 Hz, 2 H), 1.06 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 161.4, 160.0, 133.1, 129.9 (q, J = 31.3 Hz), 126.8, 123.5 (q, J = 272.5 Hz), 117.1, 113.3, 103.6, 70.0, 60.0, 30.3, 22.4, 10.4; HRMS (ESI) m/z calcd for $C_{15}H_{17}F_3NO_3$ (MH^+) 316.1156, found 316.1159.

{3-[4-(Propyloxy)-2-(trifluoromethyl)phenyl]-5-isoxazolyl}-acetic Acid (22). To 600 mL of MeCN was added 48.0 g (209 mmol) of periodic acid in portions. The mixture was stirred at room temperature for 20 min to form a clear solution, followed by addition of 30.0 g (95.0 mmol) of alcohol **21** as a solution in 50 mL of MeCN. The solution was cooled with an ice–water bath, and 394 mg (1.77 mmol) of PCC was added. A light yellow precipitate was rapidly produced. The ice bath was removed, and the reaction mixture was warmed to room temperature with stirring. After being stirred for 3 h, the mixture was concentrated by rotary evaporation to a volume of approximately 150 mL and was then diluted with 500 mL of 9/1 chloroform/*i*-PrOH. The rapidly stirred suspension was treated with 10% aqueous sodium bisulfite in portions until the color of the solution changed from brown to light green. After being vigorously stirred for an additional 20 min, the organic layer was washed with 2 × 300 mL of water and 300 mL of brine, dried over Na_2SO_4, and concentrated in vacuo to afford 27.0 g of the crude product. Trituration with 5% EtOAc in hexanes provided 23.0 g (73%) of carboxylic acid **22** as a white solid: mp 85.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.2 (bs, 1 H), 7.58 (d, J = 5.0 Hz, 1 H), 7.31 (m, 1 H), 7.11 (m, 1 H), 6.51 (s, 1 H), 4.02 (t, J = 6.0 Hz, 2 H), 3.96 (s, 2 H), 1.86 (tq, J = 6.0, 7.5 Hz, 2 H), 1.08 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 164.2, 161.5, 160.1, 133.3, 130.0 (q, J = 21.3 Hz), 123.5 (q, J = 271.3 Hz), 119.5, 117.1, 113.4 (m), 105.3, 70.1, 32.5, 22.4, 10.4; HRMS (ESI) m/z calcd for $C_{15}H_{15}F_3NO_4$ (MH^+) 330.0948, found 330.0947.

Methyl {3-[4-(Propyloxy)-2-(trifluoromethyl)phenyl]-5-isoxazolyl}acetate (23). To 250 mL of MeOH was added 25 mL of acetyl chloride at room temperature. After being stirred for 5 min, the mixture was treated with 28.5 g (86.6 mmol) of carboxylic acid **22** in portions and stirred at room temperature for 2 h. The solvent was removed in vacuo to provide 28.3 g (95% on crude) of methyl ester **23** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, J = 5.0 Hz, 1 H), 7.31 (m, 1 H), 7.11 (m, 1 H), 6.48 (s, 1 H), 4.02 (t, J = 6.0 Hz, 2 H), 3.91 (s, 2 H), 3.80 (s, 3 H), 1.86 (tq, J = 6.0, 7.5 Hz, 2 H), 1.08 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 164.8, 161.5, 160.0, 133.2, 129.9 (q, J = 31.3 Hz), 123.5 (q, J = 272.5 Hz), 119.7, 117.1, 113.3 (m), 105.0 (m), 70.1, 52.6, 32.6, 22.4, 10.4; HRMS (ESI) m/z calcd for $C_{16}H_{17}F_3NO_4$ (MH^+) 344.1105, found 344.1104.

Bis(1,1-dimethylethyl) 1-(2-(Methyloxy)-2-oxo-1-{3-[4-(propyloxy)-2-(trifluoromethyl)phenyl]-5-isoxazolyl}ethyl)-1,2-hydrazinedicarboxylate (25). A solution of 2.00 g (5.83 mmol) of acetate **23** and 1.34 g (5.83 mmol) of di-*tert*-butyl azodicarboxylate in 22 mL of DMF was cooled in an ice bath for 5 min, and 430 mg (5.83 mmol) of lithium carbonate was added in one portion. After being stirred at 0 °C for 4 h, the reaction mixture was treated with 1.0 mL (17.5 mmol) of HOAc, 45 mL of MTBE, and 20 mL of water. After being warmed to ambient temperature, the layers were separated. The organic layer was washed successively with 3 × 15 mL of water and 20 mL of brine, dried over 15 g Na_2SO_4 and concentrated in vacuo to give 3.65 g of crude product **25** as a thick oil. The crude product was treated with 2.5 mL of MTBE and 30 mL of heptanes. After being stirred and heated to near full dissolution, the mixture was cooled to ambient temperature over 5 min. An additional 15 mL of heptane was added over 35 min to the partially crystallized mixture. The mixture was stirred for 2 h, filtered, washed with 15 mL of heptanes, and dried at 48 °C to give 2.46 g (74%) of hydrazinedicarboxylate **25** as a white crystalline solid: mp 97.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (bs, 1 H), 7.13 (m, 1 H), 6.94 (m, 1 H), 5.82–6.54 (m, 3 H), 3.85 (t, J = 5.4 Hz, 2 H), 3.69 (s, 3 H), 1.70 (tq, J = 5.4, 7.5 Hz, 2 H), 1.35 (s, 9 H), 1.19–1.24 (bs, 9 H), 0.91 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 167.8, 161.2, 160.1, 133.2 (m), 123.4 (q, J = 273.8 Hz), 117.1, 113.2 (m), 106.4 (m), 82.9, 70.0, 53.2, 28.1, 28.0 (m), 27.7, 22.4, 10.4; HRMS (ESI) m/z calcd for $C_{26}H_{35}F_3N_3O_8$ (MH^+) 574.2371, found 574.2374. Anal. Calcd for $C_{26}H_{34}F_3N_3O_8$: C, 54.45; H, 5.97; N, 7.33, F, 9.94. Found: C, 54.52; H, 5.88; N, 7.28, F, 9.97.

2-(2,3-Difluorophenyl)-1*H*-imidazole (26). In a 20 L reactor were successively added 1.00 kg (7.04 mol) of 2,3-difluorobenzaldehyde, 7.0 L of *i*-PrOH, 7.0 L of water, and 4.88 kg (63.3 mol) of ammonium acetate. With the internal reaction temperature controlled at 25 °C, 3.06 kg (21.1 mol) of 40 wt % aqueous glyoxal solution was added over about 6 h via a pump. The reaction mixture changed from light yellow to orange color as glyoxal was added. The residual solids in the reaction mixture were filtered off with an additional 2 L of *i*-PrOH used to rinse the reactor. The combined filtrates were transferred back to the reactor and concentrated in vacuo with heating to about 9 L. After the temperature was adjusted to 25 °C, the mixture was treated with 3.0 L of water and 10.0 L of DCM and stirred for 30 min. Layers were separated, and 10.0 L (10.0 mol) of 1 N HCl was added to the DCM layer. After being stirred and then settled for 30 min, the layers were separated. The aqueous layer containing the product was treated with about 0.80 kg (10.0 mol) of 50 wt % NaOH to adjust the mixture to pH 7.0. The resulting slurry was cooled to 5 °C, stirred for 1 h, filtered, washed with 2.0 L of water, and dried at 50 °C to provide 1.14 kg (90%) of imidazole **26** as a gray solid: mp 158.4 °C dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.4 (s, 1 H), 7.79 (m, 1 H), 7.43 (m, 1 H), 7.30–7.07 (m, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 151.3, 151.2, 150.2 (dd, J = 243.8, 11.3 Hz), 146.6 (dd, J = 248.8, 15.0 Hz), 139.4, 125.1 (m), 123.8 (m), 120.8 (d, J = 8.8 Hz), 116.5 (d, J = 16.3 Hz); HRMS (ESI) m/z calcd for $C_9H_7F_2N_2$ (MH^+) 181.0572, found 181.0569.

(2-(2,3-Difluorophenyl)-1*H*-imidazole-4,5-diyl)dimethanol (27). In a 20 L reactor were successively added 565 g (3.14 mol) of imidazole **26**, 8.5 L of water, and 353 g (6.27 mol) of KOH. After being stirred at 25 °C for 10 min, the mixture was treated with 4.16 kg (47.0 mol) of 37 wt % aqueous formaldehyde solution in portions as follows: 1.66 kg of 37 wt % formaladehyde was added and the mixture was heated to 50 °C and stirred for 1 h; the rest of the 37 wt %

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formaladehyde was added in three 832 g portions at 1 h intervals. After all the formaladehyde was added, the mixture was stirred at 50 °C for 2 h. The mixture was cooled to 25 °C and stirred for 8 h, followed by addition of 2.83 L of pH 7.2 phosphate buffer solution and 0.57 L (0.57 mol) or more of 1 N HCl to reach pH 7.0. The resulting slurry was stirred for at least 1 h, filtered, washed with 1.4 L of water, and dried at 60 °C to provide 585 g (78%) of diol product **27** as a light yellow solid: mp 195.0 °C dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.2 (s, 1 H), 7.74 (m, 1 H), 7.41 (m, 1 H), 7.28 (m, 1 H), 4.97 (s, 1 H), 4.76 (s, 1 H), 4.54 (s, 2 H), 4.43 (s, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 150.3 (dd, J = 243.8, 12.5 Hz), 146.6 (dd, J = 250.0, 15.0 Hz), 139.4 (m), 137.8, 130.3 (m), 124.9 (m), 123.8, 120.9 (d, J = 8.8 Hz), 116.4 (d, J = 17.5 Hz), 56.2, 52.8; HRMS (ESI) m/z calcd for $C_{11}H_{11}F_2N_2O_2$ (MH^+) 241.0784, found 241.0784.

2-(2,3-Difluorophenyl)-1*H*-imidazole-4,5-dicarbaldehyde (20). *A. MnO_2 Method.* To a solution of 600 g (2.50 mol) of diol **27** in 8.0 L of methanol in a 20 L reactor was added 5.40 kg (62.2 mol) of MnO_2 at room temperature. The addition was exothermic, and the temperature rose to about 33 °C. After being cooled to about 25 °C, the mixture was stirred for 1.5 h. An additional 300 g (3.44 mol) of MnO_2 was added, and the reaction mixture was stirred for 30 min. The mixture was filtered to remove the inorganic solids, and the reactor was rinsed with about 6.0 L of methanol. The combined filtrates were transferred back to the reactor and concentrated in vacuo to 2.5 L to remove much of the methanol. About 10.0 L of isopropyl alcohol was added, and concentration of the mixture continued to about 4.0 L. The resultant solids were filtered, washed with about 2.0 L of isopropyl alcohol, and dried in vacuo at 50 °C to provide 409 g (69%) of dialdehyde **20** as a fine yellow powder: mp 296.4 °C dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.1 (s, 2 H), 7.92 (m, 1 H), 7.28 (m, 1 H), 7.18 (m, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 185.9, 154.2 (m), 154.1 (m), 150.8 (dd, J = 241.3, 12.5 Hz), 147.5 (dd, J = 255.0, 13.8 Hz), 126.2 (d, J = 7.5 Hz), 125.1, 123.7 (m), 115.0 (d, J = 17.5 Hz); HRMS (ESI) m/z calcd for $C_{11}H_7F_2N_2O_2$ (MH^+) 237.0470, found 237.0469.

*B. General Procedure for Screening of the Aerobic Oxidation of **27**.* Sequential D-optimal experimental designs were applied to identify efficacious catalysts and conditions for the oxidation of diol **27** to dialdehyde **20**. A range of commercial supported catalysts (various Pd/C, Pt/C, Ru/C, and Pt–Bi/C) were evaluated along with the effect of solvent (methanol, ethanol, acetone, acetonitrile, toluene, methyl isobutyl ketone), catalyst loading (10–100 wt %), base equivalents (0–2 equiv) and aqueous content (10–60 vol). Experiments were conducted in HPLC vials arranged in a 48-position well plate array. Each vial was equipped with a stirring bar and charged with 25 mg of diol **27** and 2.5–25 mg of catalyst using a FlexiWeigh (Mettler-Toledo Inc.) powder dispensing robot. The appropriate volume of solvent and base were added by Eppendorf pipet, as dictated by the experimental design, and each vial was crimped shut, piercing each septum with a 16-gauge needle. The plate was transferred to a Cat96 (HEL Inc.) pressure reactor, and the platewas heated at 70 °C under 3–5 bar of air with agitation for 5 h. After cooling to ambient temperature each vial was diluted with methanol and reaction conversion assessed by HPLC for the analysis of **20** and **27** and byproducts **A** and **B**. Optimization of lead conditions was conducted in an analogous manner, looking at the effect of reaction temperature, pressure, and inorganic base. See the Supporting Information for the tabulated results from the screening.

C. Optimized Aerobic Oxidation Method. To 2.00 g (8.30 mmol) of diol **27** in 58 mL of MeCN was added 5.0 mL (12.5 mmol) of 2.5 N aqueous KOH. After being stirred at room temperature for 15 min, the mixture was treated with 1.00 g of 5% Pt/5% Bi on carbon. The reaction mixture was heated to 45 °C and stirred vigorously in open air until complete in about 23 h. The solution was cooled to room temperature and filtered over a pad of Celite 545 to remove the carbon-supported metal catalyst. The Celite pad was rinsed with 40 mL of MeCN and the rinse combined with the first filtrate. The MeCN solution was concentrated in vacuo to give 2.10 g of the dialdehyde. LCMS analysis showed 85% of the bis-aldehyde **20**, 7% of the monoaldehyde **A**, and 4% of the aldehyde acid **B**. The crude product was taken to the next step without further purification (see the procedure for **1**).

2-(2,3-Difluorophenyl)-5*H*-imidazo[4,5-d]pyridazine (16). In a 20 L reactor were added a solution of 295 g (1.25 mmol) of crude dialdehyde **20** in 4.5 L of *i*-PrOH and 256 g (1.31 mol) of benzylhydrazine hydrochloride at room temperature. The mixture was stirred for 40 min, and 234 mL (0.94 mol) of 4 N HCl in 1,4-dioxane was added. After being stirred for 40 min, the resulting white slurry was filtered and dried in vacuo at 60 °C to give 393 g (88%) of the HCl salt of the *N*-benzylpyridazine intermediate.

To 52.8 g (147 mmol) of the *N*-benzyl pyridazine HCl salt in a 2 L flask was added 10.6 g of 10% Pd/carbon and 792 mL of 9/1 MeOH/water at room temperature. After being degassed and purged twice with hydrogen, the mixture was hydrogenated under an atmsopheric pressure of hydrogen at 50 °C for 5 h with vigorous stirring. The reaction mixture was cooled to room temperature, purged with nitrogen three times, and filtered through a pad of Celite 545. The Celite pad was washed with 1.1 L of 9:/1 EtOH/water, and the combined filtrates were evaporated in vacuo to 750 mL. The mixture was vigorously stirred and neutralized with about 125 mL of 1 N aqueous NaOH to pH 7.0. The resulting solids were collected by filtration. The mother liquor was further concentrated in vacuo to generate more solids from evaporation. The solids were again collected by filtration. This was repeated a third time. The combined solids were dried in vacuo at 55 °C to provide 27.5 g (80%) of product **16** as a white solid: mp 300 °C dec; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.61 (s, 2 H), 8.14 (m, 1 H), 7.61 (m, 1 H), 7.40 (m, 1 H), 7.38 (bs, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.8,150.5 (dd, J = 244.3, 11.6 Hz), 148.3 (dd, J = 255.8, 13.6 Hz), 147.3 (d, J = 13.7 Hz), 142.4, 140.1, 126.3, 124.9 (t, J = 5.9 Hz), 122.3, 119.0 (d, J = 17.1 Hz); HRMS (ESI) m/z calcd for $C_{11}H_7F_2N_4$ (MH^+) 233.0634, found 233.0633.

Methyl 2-Hydrazinyl-2-(3-(4-propoxy-2-(trifluoromethyl)-phenyl)isoxazol-5-yl)acetate (24). The screening of acids for conversion of **25** to **24** was carried out as follows. In each of the five 5 mL vials was added 50 mg (0.146 mmol) of **25**. Acids (2 mL each) were then added at room temperature as follows: 4 M HCl in 1,4-dioxane (A), 1 M HCl in HOAc (B), 33% HBr in HOAc (C), 10% aqueous H_2SO_4 (D), and 4 M aqueous HCl (E). Reactions A–E were monitored by HPLC (column Luna C_{18} 50 × 2 mm, 3 μm; mobile phase A, water (0.05% TFA); mobile phase B, MeCN (0.05% TFA); gradient, 0–95% B over 8 min; detection 220 nm; temperature 40 °C; retention time, 7.1 min for **25**, 4.3 min for **24**, 6.4 and 6.6 min for the two transient mono-BOC intermediates). The reactions were sampled for HPLC analysis after 20 min and 3 h. The 20 min samples showed amounts of **24**/**25** as follows: 21%/6% (A), 58%/0% (B), 91%/0% (C), 10%/82% (D), and 2%/77% (E). The 3 h samples showed amounts of **24**/**25** as follows: 9%/0% (A), 50%/0% (B), 87%/0% (C), 2%/71% (D), and 6%/72% (E). We concluded from those results that conditions A and B were able to convert **25** to **24** but product **24** decomposed under those conditions. Conditions D and E were too slow for the deprotection of **25**. Only condition C (33% HBr in HOAc) provided a quick reaction as well as a condition amenable to the stability of **24**. It is worth mentioning that the screening was conducted in the absence of dialdehyde **20**, which as we found out in preparation of **1** and **3** reacted immediately with **24** to form the imidazopyridazine ring under the acidic conditions.

Methyl [2-(2,3-Difluorophenyl)-5*H*-imidazo[4,5-*d*]pyridazin-5-yl]{3-[4-(propyloxy)-2-(trifluoromethyl)phenyl]-5-isoxazolyl}-acetate (1). To a mixture of 2.00 g (3.49 mol) of 1,2-hydrazinedicarboxylate **25** and 931 mg (3.94 mol) of imidazole-4,5-dicarbaldehyde **20** in 20 mL of EtOAc was added 2.5 mL (13.9 mmol) of 33 wt % HBr in HOAc at room temperature. After being stirred for 1 h, the reaction mixture was diluted with 25 mL of water. Layers were separated. The organic layer was successively washed with 20 mL of saturated aqueous $NaHCO_3$, 10 mL of saturated aqueous NH_4Cl, and 10 mL of brine, dried over Na_2SO_4, and evaporated to give 3.10 g of crude **1**. The crude product was dissolved in 5 mL of EtOAc with heating and treated with 20 mL of hexanes. After being stirred at room temperature for 3.5 h, the mixture was filtered, washed with 15 mL of

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hexanes, and dried overnight at 55 °C to give 1.68 g (84%) of methyl ester prodrug **1** as a white solid. This was recrystallized in 5 mL of EtOAc and 30 mL of hexanes to provide 1.52 g (76%) of methyl ester prodrug **1** as a crystalline solid: mp 136.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (s, 1 H), 9.32 (s, 1 H), 8.21 (t, J = 7.5 Hz, 1 H), 7.59 (d, J = 10.0 Hz, 1 H), 7.29−7.32 (m, 2 H), 7.24 (m, 1 H), 7.14 (dd, J = 10.0, 4.8 Hz, 1 H), 7.03 (s, 1 H), 6.92 (s, 1 H), 4.02 (d, J = 7.0 Hz, 2 H), 3.95 (s, 3 H), 1.86 (tq, J = 7.0, 7.5 Hz, 2 H), 1.08 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 164.4, 162.1, 161.3, 160.6, 151.5 (dd, J = 252.5, 15.0 Hz), 149.8 (dd, J = 255.8, 13.6 Hz) 148.9, 145.4, 141.9, 136.6, 133.3, 130.0 (q, J = 31.3 Hz), 126.7, 124.1 (m), 123.4 (q, J = 271.3 Hz), 122.3, 118.1 (m), 118.1, 117.2, 113.6 (m), 108.6 (m), 70.1, 68.4, 54.5, 22.4, 10.4; HRMS (ESI) m/z calcd for $C_{27}H_{21}F_5N_5O_4$ (MH^+) 574.1508, found 574.1513. Anal. Calcd for $C_{27}H_{20}F_5N_5O_4$: C, 56.55; H, 3.52; N, 12.21, F, 16.56. Found: C, 56.65; H, 3.37; N, 12.26, F, 16.73.

2-[(2-Hydroxyethyl)oxy]ethyl [2-(2,3-Difluorophenyl)-5*H*-imidazo[4,5-*d*]pyridazin-5-yl]{3-[4-(propyloxy)-2-(trifluoromethyl)phenyl]-5-isoxazolyl}acetate (2). To a solution of 300 g (5.23 mmol) of methyl ester **1** in 3.0 L of *i*-PrOAc in a 20 L reactor was added 2.78 kg (26.2 mol) of bis(ethylene glycol) and 529 g (5.23 mol) of triethylamine. The mixture was stirred at 20 °C for 3 h. The reaction was quenched with 317 g (5.28 mol) of acetic acid and treated with 3 L of brine. Layers were separated, and the *i*-PrOAc layer was washed with 3 × 3 L of water to remove excess bis(ethylene glycol) and triethylamine salts. About 1.5 L of heptane was added, followed by seed crystals and an additional 1.5 L of heptane. After the mixture was stirred for 30 min, the solid was filtered, washed with 600 mL of *i*-PrOAc/heptane (1/3) and dried in vacuo at 60 °C to give 274 g (81%) of bis(ethylene glycol) prodrug **2** as a white crystalline solid: mp 114.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1 H), 9.30 (s, 1 H), 8.18 (t, J = 7.5 Hz, 1 H), 7.56 (d, J = 10.0 Hz, 1 H), 7.21−7.31 (m, 3 H), 7.11 (m, 1 H), 7.10 (s, 1 H), 6.95 (s, 1 H), 4.51 (t, J = 5.0 Hz, 2 H), 4.00 (t, J = 7.0 Hz, 1 H), 3.79 (bs, 1 H), 3.72 (m, 4 H), 3.54 (m, 2 H), 1.85 (tq, J = 7.0, 7.5 Hz, 2 H), 1.06 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 163.8, 162.0, 161.5, 160.5, 151.4 (dd, J = 247.5, 13.8 Hz), 149.8 (dd, J = 260.0, 15.0 Hz), 148.9, 145.5, 141.9, 137.1, 133.3, 130.0 (q, J = 30.0 Hz), 126.7, 123.4 (q, J = 272.5 Hz), 124.0 (t, J = 5.6 Hz), 119.0 (d, J = 17.5 Hz), 118.9 (m), 118.2 (d, J = 2.5 Hz), 117.2, 113.5 (q, J = 6.3 Hz), 108.5 (m), 72.7, 70.1, 68.7, 68.2, 66.5, 61.4, 22.4, 10.4; HRMS (ESI) m/z calcd for $C_{30}H_{27}F_5N_5O_6$ (MH^+) 648.1876, found 648.1881. Anal. Calcd for $C_{30}H_{26}F_5N_5O_6$: C, 55.64; H, 4.05; N, 10.82, F, 14.56. Found: C, 55.82; H, 3.98; N, 10.83, F, 14.66.

4-Bromo-2-(trifluoromethyl)benzaldehyde Oxime (28). A 20 L reactor was charged with 6.5 L of MTBE and 1.40 kg of *n*-butyllithium (5.13 mol, 2.5 M in hexanes). After the solution was cooled to −5 °C, 1.30 kg (4.28 mol) of 2,5-dibromotrifluoromethylbenzene was added as a solution in 3.9 L of MTBE over 30 min with the reaction temperature kept below 25 °C. After being stirred for 30 min and with consumption of aryl bromide confirmed by HPLC as well as TLC, the mixture was treated with 344 g (4.71 mol) of DMF over about 5 min while the reaction temperature was kept below 30 °C. The reaction mixture was stirred for 20 min and quenched with 6 L of water and 1.71 L (10.3 mol) of 6 N HCl. Layers were separated, and the MTBE layer was washed with 2 × 6 L of water, concentrated in vacuo to give the intermediate aldehyde as an oil.

The crude aldehyde was diluted with 7.8 L of EtOH and treated with 339 g (5.13 mol, 50% aqueous solution) of hydroxylamine. The reaction mixture was heated to 50 °C and stirred for 1 h. After addition of 6.5 L of water, the mixture was vigorously stirred until crystallization began. Once crystallization had occurred, an additional 6.5 L of water was added and the mixture was stirred for 30 min. The solid was filtered, washed with 2.6 L of water/EtOH (1.7/1), and dried in vacuo at 65 °C to afford 966 g (84%) of oxime **28** as a crystalline solid: mp 114.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.43 (s, 1 H), 7.89 (d, J = 10.0 Hz, 1 H), 7.83 (s, 1 H), 7.80 (s, 1 H), 7.69 (d, J = 10.0 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.3, 135.2, 129.8 (q, J = 30.0 Hz), 129.2 (m), 129.1, 128.8, 123.0 (q, J = 272.5 Hz), 123.8; HRMS (ESI) m/z calcd for $C_8H_6BrF_3NO$ (MH^+) 267.9580, found 267.9583.

2-{3-[4-Bromo-2-(trifluoromethyl)phenyl]-5-isoxazolyl}-ethanol (29). To a solution of 915 g (3.41 mol) of oxime **28** in 4.6 L of DMF in a 20 L reactor was added 479 g (3.58 mol) of NCS in four portions to limit the exotherm. The mixture was stirred for 30 min and then diluted with 9 L of MTBE and 4.5 L of water. Layers were separated, and the MTBE layer was washed with 2 × 4.5 L of water.

To the MTBE solution of the intermediate chloro oxime was added 327 g (4.44 mol) of 3-butyn-1-ol and 380 g (3.76 mol) of triethylamine. The reaction mixture was stirred at 50 °C for 3 h. After being cooled to 25 °C, the mixture was treated with 9 L of water and stirred vigorously for 5 min. Layers were separated, and the MTBE layer was washed with 2 × 9 L of water, to provide 915 g (80% based on solution assay analysis) of isoxazolyl cycloadduct **29** as an MTBE solution. A small sample was evaporated to dryness to an oil for analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1 H), 7.76 (d, J = 5.0 Hz, 1 H), 7.51 (d, J = 5.0 Hz, 1 H), 6.32 (s, 1 H), 3.98 (t, J = 7.5 Hz, 2 H), 3.08 (t, J = 7.5 Hz, 2 H), 2.40 (bs, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 160.6, 135.1, 133.2, 130.3 (q, J = 32.5 Hz), 129.8 (q, J = 6.3 Hz), 127.4, 123.9, 122.8 (q, J = 272.5 Hz), 103.4, 59.9, 30.3; HRMS (ESI) m/z calcd for $C_{12}H_{10}BrF_3NO_2$ (MH^+) 335.9842, found 335.9843.

2-{3-[4-Cyclopropyl-2-(trifluoromethyl)phenyl]-5-isoxazolyl}ethanol (30). In a 20 L reactor were successively added 1.52 kg (7.14 mol) of K_3PO_4, 613 g (7.14 mol) of cyclopropylboronic acid, and 48.6 g (59.5 mmol) of 1,1′-bis(diphenylphosphino)-ferrocene−palladium(II) dichloride dichloromethane complex under a nitrogen atmosphere. A solution of 800 g (2.38 mol) of **29** in 4.8 L of 1,4-dioxane was added. The reaction mixture was heated at a rate of 1 °C/min to 90 °C. After being vigorously stirred for 1 h, the reaction mixture was cooled to 25 °C, diluted with 8 L of EtOAc and 8 L of water, and stirred for 10 min until the solids dissolved. Layers were separated, and the organic layer was successively washed with 8 L of water, 8 L of 3 N aqueous HCl, 8 L of 3 N aqueous NaOH, and 8 L of water. The organic solution was filtered and concentrated in vacuo to afford 739 g (quantitative yield of crude) of cyclopropyl product **30** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 10.0 Hz, 1 H), 7.46 (s, 1 H), 7.27 (d, J = 10.0 Hz, 1 H), 6.29 (s, 1 H), 3.99 (m, 2 H), 3.07 (m, 2 H), 2.14 (bs, 1 H), 1.99 (m, 1 H), 1.08 (d, J = 5.0 Hz, 2 H), 0.79 (d, J = 5.0 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 161.6, 146.5, 131.7, 128.8, 128.6 (q, J = 30.0 Hz), 125.2, 123.9 (q, J = 5.0 Hz), 123.8 (q, J = 272.5 Hz), 122.7, 103.6, 60.1, 30.4, 15.4, 9.9; HRMS (ESI) m/z calcd for $C_{15}H_{15}F_3NO_2$ (MH^+) 298.1050, found 298.1050.

{3-[4-Cyclopropyl-2-(trifluoromethyl)phenyl]-5-isoxazolyl}-acetic Acid (31). In a 20 L reactor were added 1.47 kg (6.46 mol) of periodic acid, 16.0 g (74.4 mmol) of pyridinium chlorochromate (PCC), and 5.93 L of MeCN. The mixture was heated to 40 °C for 1 h and cooled to 20 °C, followed by addition of a solution of 737 g (2.48 mol) of alcohol **30** as a solution in 3.1 L of MeCN slowly over a minimum of 30 min via pump. The resulting mixture was stirred for 2 h. An additional charge of 500 g (2.19 mol) of periodic acid and 10.0 g (46.0 mmol) of PCC was made, and the resulting mixture was stirred overnight (~16 h). The reaction mixture was treated with 7.4 L of water and stirred for 15 min. Layers were separated, and the organic layer was treated with 6.0 kg of 25 wt % Na_2SO_3 solution, which generated a colorless mixture. Layers were separated, and the organic layer was concentrated in vacuo, cooled to 20−25 °C, diluted with 1.5 L of MTBE, and treated with 4.4 L of 1 N NaOH. The resulting mixture was stirred for 15 min. Layers were separated, and the lower aqueous layer was returned to the reactor and acidified with 753 g (7.68 mol) of concentrated sulfuric acid. The resulting aqueous mixture was extracted with 2 × 1.7 L of toluene. The combined toluene layers were charged back into the reactor along with 4.1 L of heptanes. The resulting mixture was heated to 93 °C, and the distillate that collected during heating was discarded. The hot solution was filtered into a clean reactor through filter paper. The filtrate was cooled to 65 °C, held for 2 h, and seeded. After being cooled to −5 °C over 2.5 h, the resulting slurry was held overnight. The slurry was filtered, and the filter cake was washed with 2 × 2.2 L of heptanes and dried in vacuo at 55 °C to provide 584 g (76% yield from **29**) of carboxylic acid

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31 as a crystalline solid: mp 133.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 5.0 Hz, 1 H), 7.50 (s, 1 H), 7.31 (d, J = 5.0 Hz, 1 H), 6.51 (s, 1 H), 3.97 (s, 2 H), 2.02 (m, 1 H), 1.11 (m, 2 H), 0.81 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 164.2, 161.7, 146.7, 131.7, 128.8, 128.5, 123.7 (q, J = 272.5 Hz), 124.7, 123.9 (q, J = 6.5 Hz), 122.7, 105.3 (d, J = 2.5 Hz), 32.4, 15.4, 9.9; HRMS (ESI) m/z calcd for $C_{15}H_{13}F_3NO_3$ (MH^+) 312.0842, found 312.0844.

Methyl {3-[4-Cyclopropyl-2-(trifluoromethyl)phenyl]-5-isoxazolyl}acetate (32). To a solution of 555 g (1.78 mol) of carboxylic acid **31** in 4.5 L of methanol in a 20 L reactor was added 11.3 mL (89.2 mol) of TMSCl at room temperature. The reaction mixture was heated to 64 °C for 3.5 h, cooled to room temperature, and held overnight. The resulting solution was concentrated in vacuo to a brown oil and dried overnight at 55 °C to provide 567 g (98%) of methyl ester **32** as a light brown oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, J = 10.0 Hz, 1 H), 7.49 (s, 1 H), 7.30 (d, J = 10.0 Hz, 1 H), 6.48 (s, 1 H), 3.91 (s, 2 H), 3.79 (s, 3 H), 2.01 (m, 1 H), 1.10 (m, 2 H), 0.80 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 164.9, 161.6, 146.6, 131.7, 128.8, 128.5, 124.9 (m), 124.8, 123.9 (q, J = 5.0 Hz), 123.8 (q, J = 271.3 Hz), 104.9, 52.6, 32.6, 15.4, 9.9; HRMS (ESI) m/z calcd for $C_{16}H_{15}F_3NO_3$ (MH^+) 326.0999, found 326.1002.

Bis(1,1-dimethylethyl) 1-[1-{3-[4-Cyclopropyl-2-(trifluoromethyl)phenyl]-5-isoxazolyl}-2-(methyloxy)-2-oxoethyl]-1,2-hydrazinedicarboxylate (33). To a solution of 566 g (1.74 mol) of acetate **32** in 5.1 L of DMF in a 20 L reactor was added 389 g (1.69 mol) of di-*tert*-butyl azodicarboxylate and 64.3 g (870 mmol) of lithium carbonate at 0 °C. After being stirred at 0 °C for 1 h, the mixture was gradually warmed to 22 °C over 16 h and stirred overnight. Upon completion of the reaction, the mixture was cooled to 0 °C, diluted with 5.6 L of MTBE, quenched with 110 mL (1.91 mol) of acetic acid, and treated with 5.6 L of water. After being warmed to ambient temperature, the layers were separated. The aqueous layer was back-extracted twice with 3.4 and 2.8 L of MTBE, respectively. The combined organic layers were washed successively with 2 × 2.8 L of water and 2.8 L of saturated brine. Upon concentration to about 2.8 L at reduced pressure, the light brown solution was diluted with 2 L of heptane and seeded at ambient temperature. After being treated with 100 mL of MTBE for better stirring, the mixture was stirred overnight. The mixture was filtered and rinsed with 250 mL of MTBE and 2 × 250 mL of heptane. The filter cake was dried at 55 °C to provide a first crop of 608 g of dicarboxylate **33** as a crystalline yellow solid. The filtrate was concentrated to 524 g and diluted with 75 mL of MTBE and 250 mL of heptane. After seeding, the mixture was stirred at ambient temperature overnight, filtered, washed with 2 × 20 mL of heptanes/MTBE (2/1), and dried at 55 °C to give 145 g of a second crop of product as a crystalline solid. The total yield from the two crops was 753 g (80.3% based on input of the limiting reagent di-*tert*-butyl azodicarboxylate) of **33**: mp 93.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (bs, 1 H), 7.48 (s, 1 H), 7.28 (m, 1 H), 5.98−6.71 (m, 3 H), 3.84 (s, 3 H), 2.00 (m, 1 H), 1.51 (s, 9 H), 1.35−1.40 (bs, 9 H), 1.10 (m, 2 H), 0.80 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 162.7, 161.4, 131.7, 128.7, 128.5 (m), 127.0, 124.8 (m), 123.9 (q, J = 5.0 Hz), 123.8 (m), 123.7 (q, J = 271.3 Hz), 122.6, 106.4 (m), 82.9, 81.5, 53.2, 28.1, 28.0, 15.4, 9.9; HRMS (ESI) m/z calcd for $C_{26}H_{33}F_3N_3O_7$ (MH^+) 556.2265, found 556.2268. Anal. Calcd for $C_{26}H_{32}F_3N_3O_7$: C, 56.21; H, 5.81; N, 7.56, F, 10.26. Found: C, 56.09; H, 5.75; N, 7.52, F, 10.34.

Methyl {3-[4-Cyclopropyl-2-(trifluoromethyl)phenyl]-5-isoxazolyl}[2-(2,3-difluorophenyl)-5*H*-imidazo[4,5-*d*]pyridazin-5-yl]acetate (3). In a 20 L reactor were added 738 g (1.33 mol) of 1,2-hydrazinedicarboxylate **33**, 392 g (1.66 mol) of imidazole-4,5-dicarbaldehyde **20**, and 7.4 L of EtOAc. The mixture was cooled to 0 °C, followed by addition of 1.03 L (4.71 mol) of 33 wt % HBr in AcOH over 5 min. The reaction mixture was warmed to ambient temperature over about 1 h and stirred overnight. After being cooled to 0 °C, the mixture was treated with 5.7 L of water. Upon warming to ambient temperature, the layers were separated. The aqueous layer was back-extracted twice with 3.6 and 2.2 L of EtOAc. The combined organic layers were washed with 4.4 and 3.7 L of saturated aqueous $NaHCO_3$, followed by 3.7 L of brine. Upon concentration to about 2.8 L at reduced pressure, the light brown solution was transferred to a round-bottom flask, diluted with 250 mL of MTBE, and seeded at ambient temperature. After being stirred overnight, the mixture was filtered through a ceramic funnel and rinsed with 120 mL of MTBE and 140 mL of heptane. The filter cake was dried at 60 °C to provide a first crop of 394 g of methyl ester prodrug **3** as a crystalline yellow solid. The filtrate was concentrated to about 700 mL and diluted with 100 mL of MTBE and 80 mL of heptane. Crystallization, filtration, and air-drying gave 360 g of a second crop of product **3**. Recrystallization was carried out on the second crop by substantially dissolving the air-dried material in 250 mL of EtOAc, followed by addition of 300 mL of MTBE and 250 mL of heptanes. The mixture was stirred at ambient temperature overnight, filtered, washed with 50 mL of MTBE and 50 mL of heptane, and dried at 55 °C to give 222 g of product **3** as a crystalline solid. The total yield from the two crops was 616 g (83%) of **3**: mp 118.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.0 (s, 1 H), 9.27 (s, 1 H), 8.08 (t, J = 7.5 Hz, 1 H), 7.37 (d, J = 10.0 Hz, 1 H), 7.31−7.33 (m, 2 H), 7.20 (m, 1 H), 7.10−7.15 (m, 3 H), 6.83 (s, 1 H), 3.78 (s, 3 H), 3.21 (brs. 1H), 1.85 (m, 2 H), 0.95 (m, 2 H), 0.64 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 162.2, 161.3, 148.1, 147.5, 147.4, 144.1, 142.2, 137.2, 134.8, 131.8, 127.8 (q, J = 287.0 Hz), 126.7, 126.6, 124.8, 124.1 (m), 108.7 (m), 68.5, 54.5, 15.4, 10.1; HRMS (ESI) m/z calcd for $C_{27}H_{19}F_5N_5O_3$ (MH^+) 556.1402, found 556.1401.

Propyl {3-[4-Cyclopropyl-2-(trifluoromethyl)phenyl]-5-isoxazolyl}[2-(2,3-difluorophenyl)-5*H*-imidazo[4,5-*d*]pyridazin-5-yl]acetate (4). To a solution of 360 g (648 mmol) of methyl ester **3** in 1.8 L of *n*-PrOH in a 20 L reactor was added 328 g (3.24 mol) of triethylamine. The reaction mixture was stirred at 22 °C for 3 h. After dilution with 3.60 L of MTBE, the reaction was quenched with 194 g (3.24 mol) of AcOH and 3.6 L of water. Layers were separated, and the MTBE layer was washed with 3 × 3.6 L of water. After addition of 1 L of heptane, the MTBE/heptanes solution was filtered through 700 g of silica gel, which was further eluted with 720 mL of MTBE/heptane (2/1). The filtrates were transferred back to the 20 L reactor, diluted with 720 mL of heptane, and seeded. The solid was filtered and dried in vacuo at 60 °C to give 270 g (71%) of propyl ester prodrug **4** as a crystalline solid: mp 138.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1 H), 9.35 (s, 1 H), 8.23 (m, 1 H), 7.55 (d, J = 10.0 Hz, 1 H), 7.51 (s, 1 H), 7.23−7.34 (m, 3 H), 7.03 (s, 1 H), 6.94 (s, 1 H), 4.32 (m, 2 H), 3.38 (brs, 1 H), 2.03 (m, 1 H), 1.71 (tq, J = 5.4, 7.5 Hz, 2 H), 1.13 (m, 2 H), 0.92 (t, J = 7.5 Hz, 3 H), 0.83 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3 (m), 164.0, 162.3, 161.5, 151.6 (dd, J = 248.8, 15.0 Hz), 149.9 (dd, J = 210.0, 16.3 Hz), 149.5, 147.6, 146.2, 141.7 (m), 136.1, 131.8, 129.0, 128.7 (q, J = 31.3 Hz), 126.7, 124.8, 124.2 (q, J = 5.0 Hz), 124.0 (q, J = 5.0 Hz), 123.9, 123.7 (q, J = 272.5 Hz), 123.3, 118.8 (d, J = 16.3 Hz), 108.5, 69.8, 68.5, 21.7, 15.5, 10.2, 10.1; HRMS (ESI) m/z calcd for $C_{29}H_{23}F_5N_5O_3$ (MH^+) 584.1716, found 584.1718. Anal. Calcd for C $C_{29}H_{22}F_5N_5O_3$: C, 59.69; H, 3.80; N, 12.00, F, 16.29. Found: C, 59.41; H, 3.66; N, 11.95, F, 16.52.

2-[(2-Hydroxyethyl)oxy]ethyl {3-[4-Cyclopropyl-2-(trifluoromethyl)phenyl]-5-isoxazolyl}[2-(2,3-difluorophenyl)-5*H*-imidazo[4,5-*d*]pyridazin-5-yl]acetate (5). To a solution of 450 g (785 mmol) of methyl ester **3** in 4.5 L of EtOAc in a 20 L reactor were added 4.5 L of bis(ethylene glycol) and 794 g (7.85 mol) of triethylamine. The mixture was stirred at 40 °C for 2 h. The reaction was diluted with 4.5 L of EtOAc, quenched with 476 g (7.93 mol) of AcOH, and treated with 4.5 L of 20% aqueous NaCl. Layers were separated, and the organic layer was washed with 3 × 4.5 L of 10% aqueous NaCl to remove excess bis(ethylene glycol) and triethylamine salts. After being concentrated to 1.0 L in vacuo, the solution was filtered to remove any particles. The filtrate was transferred back to the reactor and treated with 2.7 L of heptane. The resultant solid was filtered, washed with 1 L of EtOAc/heptane (1/1), and dried in vacuo at 60 °C to provide 361 g (73%) of bis(ethylene glycol) ester prodrug **5** as a white crystalline solid: mp 124.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1 H), 9.29 (s, 1 H), 8.18 (t, J = 5.0 Hz, 1 H), 7.51 (d, J = 10.0 Hz, 1 H), 7.48 (m, 1 H), 7.23−7.31 (m, 2 H), 7.21 (m, 1 H), 7.11 (s, 1 H), 6.95 (s, 1 H), 4.50 (t, J = 5.0 Hz, 2 H), 3.80 (bs, 1 H), 3.71 (m, 4 H), 3.54 (m, 2 H), 2.00 (m, 1 H), 1.10 (m, 2 H), 0.79 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1 (m), 163.8, 162.1,

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161.6, 151.5 (dd, J = 247.5, 13.8 Hz), 149.8 (dd, J = 258.8, 15.0 Hz), 148.9 (m), 148.8, 147.4, 145.5, 141.8, 137.1, 131.7, 128.9, 128.6 (q, J = 30.0 Hz), 126.6, 124.1, 124.0 (q, J = 6.3 Hz), 123.5, 123.4 (m), 119.0 (d, J = 16.3 Hz), 123.7 (q, J = 272.5 Hz), 108.4 (d, J = 3.8 Hz), 72.7, 68.7, 68.2, 66.5, 61.4, 15.4, 10.1; HRMS (ESI) m/z calcd for $C_{30}H_{25}F_5N_5O_5$ (MH^+) 630.1770, found 630.1775. Anal. Calcd for $C_{30}H_{24}F_5N_5O_5$: C, 57.24; H, 3.84; N, 11.12, F, 15.09. Found: C, 57.38; H, 3.72; N, 11.17, F, 15.11.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving NMR spectra for all new compounds and a table giving results for catalyst screening on oxidation of **27** to **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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